

Marco Buiatti

The Correlated Nature of Large-scale Neural Activity Unveiled by the Resting Brain

1. Introduction
2. Coherent Spatiotemporal Patterns of Spontaneous Activity
3. Resting State Networks
4. Neural Dynamics I: Brain Rhythms
5. Neural Dynamics II: Fractal Brain Dynamics
6. Neural Dynamics Associated to Resting State Networks
7. Spontaneous Activity and Behaviour
8. Discussion

Abstract. *Most of functional neuroscience studies investigate the brain's response to a task or stimulus. However, the brain is very active even in the absence of an external or internal input. Recent neuroimaging, electrophysiological and optical imaging studies revealed that the neural activity at rest is structured in functionally specific, temporally correlated, spatially distributed patterns that explain a large part of the variability of event-related responses. These results importantly extend the focus of cognitive neuroscience from the stimulus-evoked responses to the spatial and temporal correlations between different neural populations. I argue that integrating the correlated nature of the neural activity to standard measures of evoked responses might significantly advance our understanding on the neural mechanisms underlying cognitive functions. This perspective may be tackled by identifying spontaneous spatiotemporal patterns of neural activity at rest and tracking their evolution and dynamical interactions during cognitive processing.*

1. INTRODUCTION

Cognitive neuroscience addresses the question of how cognitive functions are produced by the neural circuitry of the brain. Nowadays, a wide range of experimental techniques (Table 1) may be used to pursue this question by exploring the neural activity at multiple spatial and temporal scales. Most cognitive neuroscience experiments that make use of these techniques are designed following the typical strategies of cognitive psychology, namely investigating the brain's responses to carefully controlled sensory, cognitive and motor events (Posner and Raichle [1998]). This approach has been very successful in characterizing the brain regions and neural dynamics underlying many sensory and cognitive processes.

From a theoretical standpoint, this approach fits well with a view of brain function for which brain is primarily reflexive, driven by the momentary demands of the environment. However, recent research has shown that stimulus-evoked responses typically account for less than 5% of cerebral metabolism (Raichle and Mintun [2006]). This observation supports an alternative view assuming that the brain's operations are mainly intrinsic involving the maintenance of information for interpreting, responding to and even predicting environmental demands (Raichle and Snyder [2007]). In fact, evidence of the remaining 95% of brain metabolism already emerged from the very first electroencephalography (EEG) recordings in humans (Berger [1929]), showing a remarkable electrical activity in the form of bursts of 10 Hz oscillations even in the absence of any stimulation. Probably due to the difficulty in evaluating its behavioural relevance and lack of modern imaging methods like functional Magnetic Resonance Imaging (fMRI) and optical imaging, the non-stimulus-evoked brain activity has been overlooked for decades. Recent advances in electrophysiological (Arieli *et al.* [1996], Kenet *et al.* [2003], Rodriguez *et al.* [1999], Linkenkaer-Hansen *et al.* [2001]) and neuroimaging (Biswal *et al.* [1995], Raichle *et al.* [2001]) studies provoked a re-assessment of its importance in brain function.

By reviewing numerous studies using different methodologies (Table 1), here I propose a journey on the neural activity of the brain at rest starting from single neurons, travelling across differ-

ent spatial and temporal scales and ending with an overall picture of brain-wide neural patterns. I will argue that these studies produce an important breakthrough in the general view on the neural activity by showing that such activity is structured in functionally relevant highly correlated spatiotemporal patterns, and is thus much less unpredictably variable than previously thought. I will then suggest that integrating this view into cognitive neuroscience research will significantly increase our understanding on brain functioning, and present some proposals to advance in this direction.

Table 1 – Neuroimaging methodologies

Method	Signal	Spatial extent	Spatial resolution	Temporal resolution
SUA	Spiking Activity	Single neuron	Single neuron	1 ms
LFP	Subthreshold Synaptic Activity	0.5 mm	0.5 mm	1 ms
VSDOI	Membrane Potential	3-10 mm	1 mm	1 ms
EEG/MEG	Electric/Magnetic field	Whole scalp	1-10 cm	1 ms
fMRI	Hemodynamic activity	Whole brain	1-10 mm	0.5-4 s

Basic properties of the main neuroimaging methodologies currently used in systems and cognitive neuroscience. First column: Method name. Abbreviations indicate Single-Unit Activity, Local Field Potential, Voltage-Sensitive Dye Optical Imaging, Electroencephalography/Magnetoencephalography, and functional Magnetic Resonance Imaging, respectively. Second column: Measured signal. Third column: Spatial extent of the recorded neural region. Third column: Signal spatial resolution. Fourth column: Signal temporal resolution.

A note on terminology: depending on the methodology and theoretical approach used to investigate it, the brain activity in the absence of any stimulation has been named in many ways, the most popular being ‘spontaneous’, ‘endogenous’, ‘intrinsic’. This terminology is potentially ambiguous because it might suggest that such activity is generated by the brain independently of experience, and is intrinsically distinct from the one evoked by external events. Here I will consider these adjectives as synonyms, meaning ‘not evoked by external stimulations’, but with no further claim on the

origin and nature of such neural activity. Generation of the spontaneous activity and its interaction with evoked responses are two exciting research fields that have still to be extensively explored.

2. COHERENT SPATIOTEMPORAL PATTERNS OF SPONTANEOUS ACTIVITY

Many neurons in the nervous system of invertebrate and vertebrate animals fire action potentials even in the absence of a stimulus (Alving [1968], Hausser *et al.* [2004]). This activity is typically called ‘spontaneous’, in contrast with the activity evoked by a stimulus. When a stimulus is presented repeatedly, the variability of the neural evoked responses is often as large as the response itself (Arieli *et al.* [1996]). For a long time, both the spontaneous activity and the variability of the evoked response have been considered noise, namely an intrinsic, unavoidable nuisance for cortical processing that the brain may overcome by averaging over a large number of neurons. This view considerably changed when Arieli *et al.* [1995, 1996] recorded with voltage-sensitive dye optical imaging and concurrent electrophysiology both the spontaneous and visually evoked neural activity of the cat visual cortex. While electrophysiology techniques measure neural discharges and local field potentials in proximity of the electrode (Table 1), optical imaging provides a spatiotemporal signal tracking the neural activity of an entire cortex patch (Figure 1). Far from being random, this spatiotemporal signal evolved in spatially distributed, slowly changing coherent patterns both with and without visual stimulation. As expected, responses evoked by a visual stimulus (moving gratings with variable orientation) displayed a large inter-trial variability. Notably however, single-trial spatiotemporal patterns could be predicted by summing the trial-averaged evoked response and the ongoing activity preceding the stimulus in that trial (Arieli *et al.* [1996]) (Figure 1). Response variability was thus largely explained by the fluctuations of the ongoing activity. Moreover, in a similar experiment Tsodyks *et al.* [1999] showed that single-neuron firing, far from being an independent process, was strictly determined by the surrounding spatiotemporal pattern of

neural activity, suggesting that firing variability is not at all an intrinsic property of the neuron, but largely depends on the fluctuations of the ongoing activity of the surrounding neural network.

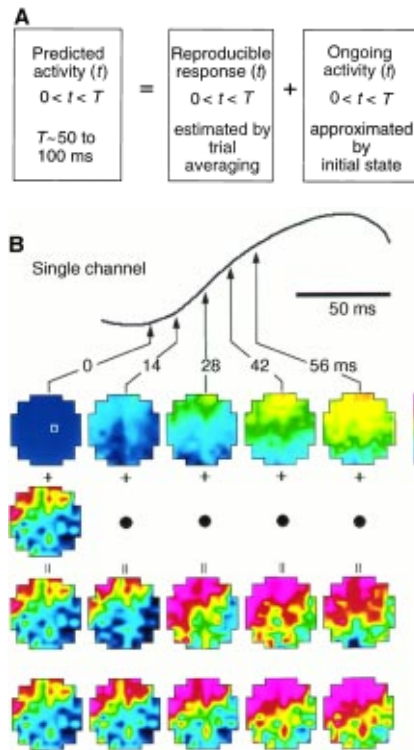


Figure 1 – Predicting the cortical evoked response from the spontaneous activity in the cat visual cortex (Arieli *et al.* [1996]). (A) A single-trial response to a stimulus was predicted by summing the reproducible response and the ongoing activity, approximated by the initial state. (B) Comparison of the predicted and measured responses. The images show the activity in a 2x2 mm area of the cortex. Top trace: Averaged evoked response (34 trials), measured from a single optical channel above the microelectrode site (small square in top-left frame). First row: Averaged evoked activity pattern (after subtraction of frame 0), shown at five different times after response onset, indicated by the arrows. All other rows show single-trial responses. Second row: Initial state, approximating ongoing activity during the response. Third row: Predicted response, obtained by adding the frames in the first and second rows. Fourth row: Measured response. Figure modified from Arieli *et al.* [1996].

Kenet *et al.* [2003] further showed that the coherent spatio-temporal patterns of spontaneous activity tracked by optical imaging

are not random, but switch across a limited number of spatiotemporal configurations. Remarkably, most of these configurations correspond closely to the ones obtained by visual stimulation with oriented bars, namely they are tuned to a specific orientation. This spontaneous switching is function-dependent: spatiotemporal patterns smoothly change in time between configurations representing similar orientation angles. Moreover, the set of spatiotemporal configurations is biased toward vertical and horizontal orientation, supporting the idea that its formation is shaped by experience. These results suggest the intriguing hypothesis that visual perception might depend on whether a map coding for a specific stimulus is already present in the set of spontaneous cortical states, and on how functionally close to that stimulus is the cortical state at the stimulus arrival.

In summary, the spontaneous activity at the neural population level is spatiotemporally correlated, has a functional architecture and largely determines single neurons' response. Cortical responses to sensory stimulation are thus not deterministic responses buried in uncorrelated noise, but the result of the interaction between the sensory input and the current cortical state.

3. RESTING STATE NETWORKS

A natural question arising from the neurophysiological studies described above is whether the spontaneous activity is organized in coherent spatiotemporal patterns also at a larger scale and in regions other than the visual cortex. The first evidence for this hypothesis came from Biswal *et al.* [1995], who showed that low frequency (<0.1 Hz) spontaneous fluctuations of Blood-Oxygen-Level Dependent (BOLD) contrast (the signal recorded by fMRI) measured in the left somatomotor cortex (LMC) are temporally correlated with spontaneous fluctuations in the right somatomotor cortex (RMC) and with medial motor areas in the absence of overt motor behaviour. Biswal *et al.* [1995] thus identified what has been later called a Resting State Network (RSN), a network of brain regions spontaneously fluctuating together at rest at very low temporal frequency. Crucially, this network has a functional signa-

ture since its regions are all associated with motor function.

Building on Biswal *et al.* [1995]’s results, Fox *et al.* [2006] showed that the inter-trial variability of event-related BOLD responses in the human brain is influenced by fluctuations of the spontaneous BOLD activity likewise evoked responses in the cat visual cortex are influenced by the local spontaneous activity (Arieli *et al.* [1996]). For this purpose, Fox *et al.* [2006] showed that the BOLD spontaneous activity measured in the RMC explains most of the variability of LMC BOLD responses following right-handed button presses. This is clearly illustrated in Figure 2: while the raw event-related responses in the LMC after button press display a large variability (panel (a)), this variability is significantly reduced (panel (c)) after subtracting the corresponding activity in the RMC after button press (panel (b)). The flat event-related response in the RMC (thick line in panel (b)) is consistent with the hypothesis that the activity in that region is independent of the motor task.

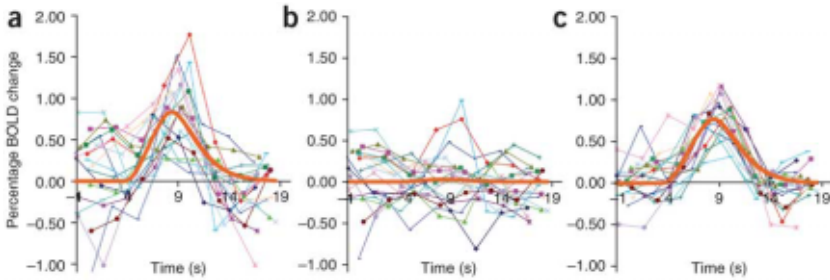


Figure 2 – Predicting the cortical evoked response from the spontaneous activity in the human somatomotor system (Fox *et al.* [2006]). (a) Raw event-related responses in the LMC for 18 button presses from a single subject. (b) The corresponding activity in the RMC for each button press. (c) Task-related responses in the LMC after subtraction of spontaneous fluctuations measured in the RMC. The thick line in each graph represents the best fit gamma function to all data points. Figure modified from Fox *et al.* [2006].

Both Arieli *et al.* [1996]’s and Fox *et al.* [2006]’s studies suggest that measured neuronal responses are the result of a linear superposition of task-evoked neuronal activity and ongoing spontaneous activity, implying no interaction between the two activi-

ties. Whether this lack of interaction also holds for neuronal responses in cortical regions dedicated to higher level cognitive processing is an interesting open question. Future experiments may pursue this question by investigating whether and at which level of cerebral processing a drop in linearity emerges between the evoked and spontaneous activity (see also the Discussion).

Biswal *et al.* [1995]'s seminal work paved the way to the identification and functional characterization of a large set of RSN in the human brain. Since the first studies, it clearly emerged that RSN display robust, highly reproducible properties as they exhibit high spatial consistency across subjects (Damoiseaux *et al.* [2006], Beckmann *et al.* [2005]) and even across species (Vincent *et al.* [2007]), can be identified in as short as 4 minutes of fMRI recordings (Mantini *et al.* [2007]), and typically share a common very slow (0.01 - 0.1 Hz) temporal course (Biswal *et al.* [1995], Fox and Raichle [2007]). Interestingly, many RSN have a natural functional interpretation, as each of them gathers brain regions typically involved in a common function during goal-directed tasks. Figure 3 illustrates a typical set of RSN, obtained by applying Independent Component Analysis (an unsupervised algorithm that identifies networks that are maximally independent of each other by minimizing a measure of mutual information) to fMRI data acquired on human subjects at rest (Beckmann *et al.* [2005]). The set in Figure 3 encompasses a network dedicated to primary visual processing (a), regions involved in visual attention (b), the auditory system (c), the sensory-motor system (corresponding closely to the RSN identified by Biswal *et al.* [1995]) (d), a visuo-spatial system with anomalous functional properties (see below) (e), regions involved in executive control (f), regions involved in the dorsal visual stream (g, h). For an extensive review on the properties of BOLD spontaneous activity and RSN, see Fox and Raichle [2007].

The brain network in panel (e) has an original story. It emerged indirectly, in the attempt to solve a baseline problem very common to event-related studies. An unexplained phenomenon was the appearance of activity decreases in functional neuroimaging data during goal-directed tasks when the control state was passive visual fixation or eyes closed resting. Intriguingly, this effect was remarkably consistent across a wide variety of task conditions.

Using PET, Raichle *et al.* [2001] suggested that these activity decreases imply the existence of a Default Mode Network (DMN) of brain activity which is active during rest and ‘switches off’ when subjects are involved in a task. Raichle *et al.* [2001] identified the DMN by comparing the brain activity at baseline with that during a wide variety of tasks. Greicius *et al.* [2003] later demonstrated that the DMN is a RSN (corresponding closely to the network in Figure 3, panel (e)) by showing that DMN areas are linked by robust positive correlations, whereas they are negatively correlated with regions activating during a simple visual task, suggesting a mechanism for attenuation of DMN activity during cognitive processing. However, the functional role of the DMN is still poorly understood (an extensive discussion on the DMN is reported in Raichle and Snyder [2007]).

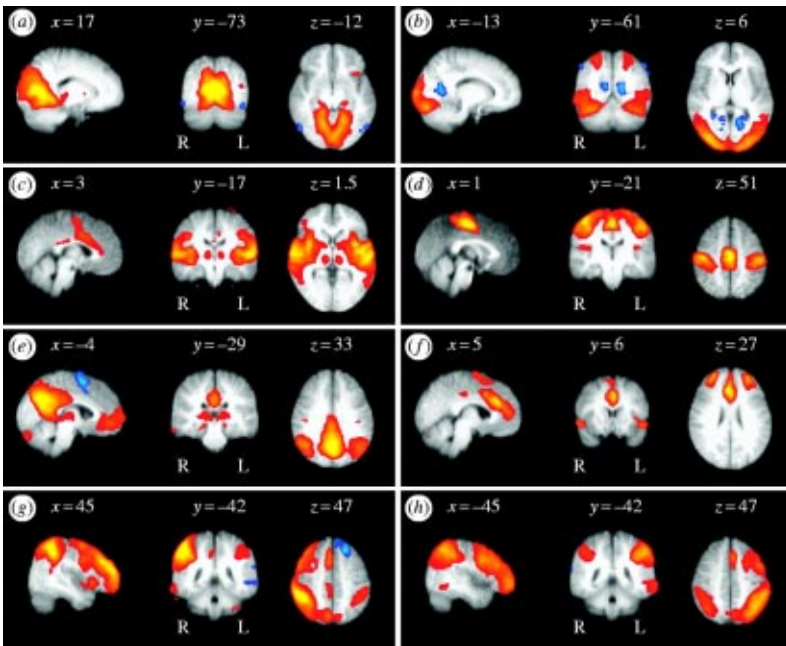


Figure 3 – Resting state networks in the human brain estimated with Independent Component Analysis (Beckmann *et al.* [2005]). Sagittal, coronal and axial views of different spatial maps associated with low-frequency resting patterns estimated from a group of 10 subjects. The coordinates refer to mm distances from the anterior commissure and images are shown in radiological convention. See the text for a functional interpretation of each network. Figure modified from Beckmann *et al.* [2005].

In summary, the BOLD activity in the human brain at rest is organised in slowly fluctuating, functionally specific distributed networks that explain a large part of the trial-by-trial variability in the event-related responses. These observations support the idea that the brain is really never ‘at rest’, and indeed devotes an important part of its functioning to the maintenance and elaboration of information accumulated by previous experience for better responding to future environmental demands.

4. NEURAL DYNAMICS I: BRAIN RHYTHMS

The existence of coherent spatiotemporal patterns of spontaneous activity is known in the EEG literature since the first electroencephalographic recordings showing clear trains of alpha (≈ 10 Hz) oscillations (Berger [1929]). Berger also showed that the alpha rhythm, very pronounced in most subjects at rest with closed eyes, decreases when subjects perform a task or simply open the eyes, illustrating the most evident example of modulation of the ongoing activity by sensory or cognitive processing. Since Berger’s pioneer studies, evidence accumulated that the neural electric activity recorded at the scalp is dominated by ‘endogenous’ rhythms that are modulated by sensory and cognitive processing (Pfurtscheller and Da Silva [1999]), but persist in the absence of a task. Rhythm amplitude is quantified by the amplitude of the envelope of oscillations at specific frequency bands, hereafter indicated as band-limited power (BLP).

These observations led to the hypothesis that oscillations might serve the purpose of neural communication between neural populations by synchronization of their oscillating activity (Varela *et al.* [2001]). These dynamic links may be established at multiple frequencies depending on the level of integration: local interactions, characterized by communication delays of 10-30 ms, may consist in synchronization in the gamma (30-100 Hz), while large-scale integration involving longer delays may be mediated by synchronization waves extending to the beta band (13-30 Hz) (Varela *et al.* [2001]). A growing body of experimental evidence confirms these predictions. It has been proved that neuronal interactions in

the cat and monkey visual cortex effectively occur through neural synchronization (Womelsdorf *et al.* [2007]). Local gamma synchrony has been observed in a wealth of tasks ranging from object representation (Tallon-Baudry *et al.* [1996]) to selective attention (Womelsdorf and Fries [2007], Doesburg *et al.* [2007]). Tasks involving large-scale integration processes of conscious access have been found to trigger large-scale synchronization in the beta band (Tallon-Baudry *et al.* [2001], Gross *et al.* [2004], Sehatpour *et al.* [2008]) and in the gamma band (Rodriguez *et al.* [1999], Miltner *et al.* [1999], Melloni *et al.* [2007]). One example is presented in Figure 4 (Melloni *et al.* [2007]) showing patterns of BLP and synchronization in the gamma band (50-57 Hz) following a masked

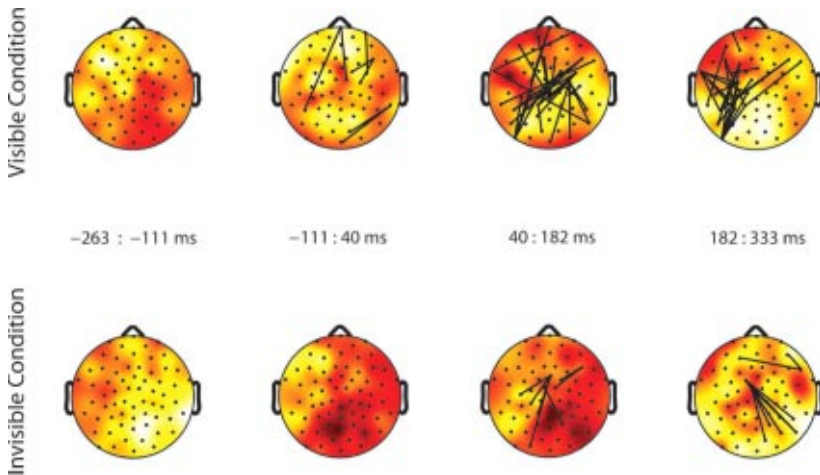


Figure 4 – Large-scale neural synchronization correlates with conscious perception (Melloni *et al.* [2007]). Scalp topography of induced gamma power and phase synchrony for the visible and invisible condition of the experiment performed by Melloni *et al.* [2007] (see more details in the text). Top row, Visible condition. Bottom row, Invisible condition. The background shades indicates induced gamma power averaged in a 50–57 Hz frequency range. Each head represents the average of a 150 ms time window. Time 0 indicates the onset of the sample word. Lines connect pairs of electrodes displaying significant synchronization. Gamma activity does not statistically differ between visible and invisible conditions. In contrast, phase synchrony is stronger in the visible condition during the 40–180 ms time window involving occipital, parietal, and frontal electrodes, with intrahemispheric and inter-hemispheric connections. In the window between 180 and 330 ms, the pattern of phase synchrony lateralizes over the left hemisphere and restricts to occipitoparietal electrodes. Figure modified from Melloni *et al.* [2007].

word that could be either visible (top row) or invisible (bottom row) during a delayed match-to-sample task. While modulations in the BLP (background topography) are similar in the two conditions, conscious perception of the word in the visible condition (first row) triggers a large-scale wave of synchronization that is missing in the other condition.

5. NEURAL DYNAMICS II: FRACTAL BRAIN DYNAMICS

However, the EEG signal is more complex than a set of band-limited oscillations. The EEG power spectrum displays clear $1/f$ -like behaviour, i.e. power increases as a power law in function of decreasing frequency. This property is the signature of scale invariance, the hallmark of fractal systems: the dependence of the signal on its past is the same irrespective of the time resolution at which the signal is observed. Scale invariance implies that oscillations at different frequencies are not independent, but reciprocally interact within an organized scale-free structure. Direct evidence for temporal long-range fractal-like correlations emerged from studies on the raw EEG (Buiatti *et al.* [2007]), and on the BLP in the alpha and beta frequency band (Linkenkaer-Hansen *et al.* [2001]). A complex dynamics also emerges from the spatial patterns of synchronization over the scalp at rest, characterized by a small-world topology typical of complex systems (Bassett *et al.* [2006]). Such topology is also scale-invariant because it does not change across frequency bands between 2 and 37 Hz (Bassett *et al.* [2006]). Crucially, temporal fractal-like correlations are modulated but not disrupted by external stimuli like somatosensory stimulation (Linkenkaer-Hansen *et al.* [2004]) or performance feedback (Buiatti *et al.* [2007]), and the small-world structure of synchronization patterns is also preserved during a task (Bassett *et al.* [2006]).

It is not clear yet whether and how this correlated structure is relevant for brain function. A general, yet unproved explanation is that a system endowed with multi-scale endogenous dynamics may optimally respond and adapt to a wide variety of external demands, while systems displaying band-limited activity may become unstable or not respond at all (Linkenkaer-Hansen *et al.* [2001],

Buiatti *et al.* [2007]). Advances in this direction might shed new light on the global organization of brain dynamics.

In summary, the dynamics of the brain electrical activity is characterized by ongoing oscillations in a wide frequency range embedded in a task-independent scale-invariant dynamical structure. This dynamics is modulated by external events, but is preserved during rest. Evidence is accumulating that ongoing oscillations are instrumental to cognitive processing because they subserve synchronization, a fundamental mechanism of neural communication that underlies local processing as well as large-scale integration among distant brain areas. The complex dynamics of this activity further suggest that interactions between slow and fast rhythms may also have an important, yet poorly explored role in brain function (Jensen and Colgin [2007]).

6. NEURAL DYNAMICS ASSOCIATED TO RESTING STATE NETWORKS

What is the neural dynamics associated to RSN? Is there a direct link between the slowly fluctuating RSNs emerged from fMRI at rest (Biswal *et al.* [1995], Greicius *et al.* [2003], Mantini *et al.* [2007]), the coherent spatiotemporal patterns identified at the neural population level by LFP and optical imaging (Arieli *et al.* [1996], Kenet *et al.* [2003]), and the complex ongoing dynamics emerging from EEG/MEG recordings (Berger [1929], Varela *et al.* [2001])? First evidence in this direction comes from the analysis of temporal fluctuations of LFPs recorded from multiple electrodes in the visual cortex of the monkey during different behavioural states (Leopold *et al.* [2003]). Surprisingly, the component of the neural signal that showed the most significant correlations across the neural population was not the raw signal, which is almost independent between neurons within a few mm, but the BLP at several frequency bands between 1 Hz and 100 Hz. BLP displayed fluctuations at many time scales, with particularly large amplitude at very low frequencies (<0.1 Hz), namely in the same spectral range of typical fluctuations of RSNs. These fluctuations exhibited high coherence between electrode pairs, particularly for the gamma

frequency range, decaying very slowly with cortical distance. Moreover, the structure and coherence of oscillation amplitudes were highly similar under distinctly different behavioral states. The spatiotemporal properties of these signals suggest that they may crucially contribute to the RSNs identified by the BOLD signals.

These observations have been recently validated and extended in two studies taking advantage of epileptic subjects with implanted electrodes covering a large part of the sensorimotor cortex (He *et al.* [2008]), and positioned bilaterally in auditory cortices (Nir *et al.* [2008]). Both studies find that BLP in the gamma band displays slow $1/f$ decaying temporal fluctuations and, crucially, robust temporal correlation within the same functional network (within the sensorimotor cortex (He *et al.* [2008]) and between hemispheres within the auditory cortex (Nir *et al.* [2008])), while no significant correlations with functionally distinct cortical areas. He *et al.* [2008] also find significant correlations in the delta (1-4 Hz) band that, contrary to gamma band, are preserved during NREM sleep.

The neural dynamics of the RSNs has also been investigated directly by simultaneously recording fMRI and EEG. Using the BLP of EEG oscillations in several frequency bands as a regressor for fMRI analysis, Laufs *et al.* [2003] found that EEG BLP in the beta band (13-30 Hz) was significantly correlated with a set of regions largely overlapping with the DMN, while, consistently with Berger [1929]'s observations, alpha desynchronization correlated with an attentional network. Crucially, the same networks also emerged from a functional connectivity analysis of the BOLD signal at rest, confirming that these EEG signatures identified functionally connected networks rather than a set of independently varying regions.

However, the assumption that the activity of a specific cerebral functional network is characterized by a single brain rhythm at a specific frequency is unlikely. Detailed biophysical studies reveal that even single neurons exhibit complex dynamics, including the capacity to oscillate at multiple frequencies (Buzsaki and Draguhn [2004]). Consistently, brain regions do not generally exhibit pure oscillations, but as mentioned above display a $1/f$ power spectrum in either the LFP (Leopold *et al.* [2003]), the BOLD signal (Zarahn

et al. [1997]) or the EEG/MEG signal (Linkenkaer-Hansen *et al.* [2001]). Furthermore, several rhythms can coexist in the same area or interact among different structures (Varela *et al.* [2001], Jensen and Colgin [2007]). Following this line of thinking, Mantini *et al.* [2007] sought for complex spectral signatures of RSN by correlating RSNs with BLP at several frequency bands extracted from concurrent EEG recordings. RSN's electrophysiological signatures were unique combinations of five rhythms, where each combination was never a pure frequency. This result shows that indeed the activity of RSN cannot be simply associated to a single frequency band, and suggests that cross-frequency interactions should be further explored to better understand RSN dynamics.

7. SPONTANEOUS ACTIVITY AND BEHAVIOUR

Since the trial-by-trial variability of brain responses can be explained by the single-trial fluctuations of spontaneous activity, one may ask whether it is possible to predict single-trial behaviour from the prestimulus spontaneous activity, especially in ambiguous situations in which behaviour is apparently random. To address this question, Hesselmann *et al.* [2008] recorded the brain activity with fMRI in subjects who reported perceptual decisions on an ambiguous figure, Rubin's vase-faces picture. Prestimulus activity in the fusiform face area, a cortical region preferentially responding to faces, was higher when subjects subsequently perceived faces instead of the vase, suggesting that fluctuations in the spontaneous activity indeed bias subsequent perceptual decisions. In another experiment, Fox *et al.* [2007] demonstrated a close relationship between the spontaneous human brain activity in the left somatomotor cortex and trial-by-trial variability in button press force.

Similar results were found in EEG experiments: for example, gamma band oscillatory activity in a frontoparietal network before stimulus onset predicts reaction time during a simple visuomotor task (Gonzalez Andino *et al.* [2005]), and ultraslow (0.01-0.1 Hz) oscillations predict behavioural performance during a somatosensory detection task (Monto *et al.* [2008]). The latter result is intriguing because the time scale of the fluctuations predicting be-

havioural performance is typical of RSN fluctuations, suggesting – again – a link between the two.

8. DISCUSSION

Deciphering the properties of the neural spontaneous activity at rest has provided a fundamental breakthrough in the general view on the neural activity: far from being random, the neural activity is composed of highly structured spatiotemporal patterns that explain a large part of the apparent variability seen in evoked responses, from the single neuron level (Arieli *et al.* [1996]) to the system's level (Fox *et al.* [2006]). These spatiotemporal patterns are spatially distributed across functionally related areas, and dynamically fluctuate at multiple frequencies, fast ones (1-100 Hz) embedded in very slow ones (0.01-0.1 Hz) in a complex dynamic structure (Varela *et al.* [2001], Linkenkaer-Hansen *et al.* [2001]). This spatiotemporal structure is extremely robust, since it's consistent across subjects (Damoiseaux *et al.* [2006]), and even across species (Vincent *et al.* [2007]).

Crucially, investigations of the neural activity at rest provided multiple evidence that the spontaneous activity is intrinsically linked with brain function: 1) spontaneous activity at the neural population level dynamically switches among a limited set of configurations that resemble the ones evoked by sensory stimulation (Kenet *et al.* [2003]), 2) functionally related areas generally belong to the same RSN (Biswal *et al.* [1995], Greicius *et al.* [2003], Fox and Raichle [2007]), 3) spontaneous activity predicts behaviour in functionally meaningful ways (Fox *et al.* [2007], Hesselmann *et al.* [2008], Monto *et al.* [2008]), 4) neural communication within and between distant cortical areas is likely to occur by synchronization of ongoing spontaneous oscillations (Varela *et al.* [2001]).

These results suggest that it's time to systematically incorporate the correlated nature of the neural activity into the research of the neural mechanisms underlying cognitive functions. This perspective may be afforded by advancing in two directions.

8.1 *Dynamic Interactions between Resting State Networks*

As previously stated, putative mechanisms of large-scale integration in the brain are synchronization and/or cross-frequency interactions of ongoing oscillations between distant brain areas (Varela *et al.* [2001], Jensen and Colgin [2007]). However, little is known about the interactions occurring within and between RSNs, and whether the brain networks interacting during large-scale integration when performing a task are the same RSNs identified at rest. These hypotheses may be investigated by identifying the dynamical patterns of ongoing oscillations associated to RSNs at rest, and tracking their interaction during a task.

The most promising methodological approach for this purpose is multimodal imaging, in particular simultaneous EEG-fMRI, a methodology that potentially tracks the whole spatiotemporal evolution of the cerebral patterns (Debener *et al.* [2006]) by combining the temporal resolution of EEG with the spatial resolution of fMRI (Table 1). A methodological development will be required to correlate measures of phase synchronization (Varela *et al.* [2001]) and cross-frequency interactions (Jensen and Colgin [2007]) with simultaneously recorded fMRI signals. Moreover, it may be possible to elucidate the neural substrates of scale-invariant correlations (Linkenkaer-Hansen *et al.* [2001], Buiatti *et al.* [2007]) and small-world network topology of synchronization patterns (Bassett *et al.* [2006]), which will be crucial to better understand the global organization of brain dynamics.

8.2 *Interactions between the Spontaneous Activity and Event-related Responses*

As previously mentioned, there is increasing evidence that single-trial evoked responses (Arieli *et al.* [1996], Fox *et al.* [2006]) and behaviour (Hesselmann *et al.* [2008], Fox *et al.* [2007], Monto *et al.* [2008]) can be partially predicted by the spontaneous activity preceding the task. These results suggest that it might be interesting to systematically track the spontaneous activity during cognitive processing in a variety of tasks for multiple purposes: 1) have a more accurate estimate of the evoked response, 2) critically advance our understanding on the functional causes of response and performance variability, 3) investigate at what level spontaneous

and evoked activity interact. As previously suggested, the latter point may be investigated by studying at which level of cognitive processing the additivity shown by Arieli *et al.* [1996] and Fox *et al.* [2006] between spontaneous and evoked activity does not hold anymore (see Hesselmann *et al.* [2008] for a first evidence of non-linear interaction). Tasks for this latter purpose may involve cognitive processes characterized by relatively long time scales, because they are more likely to interact with the slow fluctuations of the spontaneous activity.

To conclude, the view emerging from the studies reviewed in this article is that the brain activity is a mixture of variability and correlated spatiotemporal patterns, both at rest and during cognitive processing. Rather than being in conflict, these two complementary aspects of the brain activity might be fundamental for efficient adaptation to environmental changes while keeping the memory of the past experience. In this respect, the brain activity has a very similar organization to that of other living systems (Buiatti and Buiatti [2008]). I have argued that the correlated component of the neural activity might be used to advance our understanding on the neural mechanisms underlying cognitive functions. This perspective may be afforded by characterizing the ways different spontaneous spatiotemporal patterns interact with each other, and tracking their evolution during task performance. Combining the spatial resolution of fMRI and the temporal one of EEG or alternative electrophysiological measures will be determinant to pursue such plan.

*Center for Mind/Brain Sciences, University of Trento
Via delle Regole 101, 38060 Mattarello (TN), Italy*

REFERENCES

- Alving, B. [1968], Spontaneous Activity in Isolated Somata of Aplysia Pacemaker Neurons. *J. Gen. Physiol.* 51: 29-46.
- Arieli, A., D. Shoham, R. Hildesheim and A. Grinvald [1995], Coherent Spatiotemporal Patterns of Ongoing Activity Revealed by Real-Time Optical Imaging Coupled with Single-Unit Recording in the Cat Visual-Cortex. *J. Neurophysiol.* 73: 2072-2093.
- Arieli, A., A. Sterkin, A. Grinvald and A. Aertsen [1996], Dynamics of Ongoing

- Activity: Explanation of the Large Variability in Evoked Cortical Responses. *Science* **273**: 1868-1871.
- Bassett, D.S., A. Meyer-Lindenberg, S. Achard, T. Duke and E. Bullmore [2006], Adaptive Reconfiguration of Fractal Small-world Human Brain Functional Networks. *Proc. Natl. Acad. Sci. USA* **103**: 19518-19523.
- Beckmann, C.F., M. DeLuca, J.T. Devlin and S.M. Smith [2005], Investigations into Resting-state Connectivity Using Independent Component Analysis. *Philos. T. Roy. Soc. B* **360**: 1001-1013.
- Berger, H. [1929], On the EEG in Humans. *Arch. Psychiatr. Nervenkr.* **87**: 527-570.
- Biswal, B., F.Z. Yetkin, V.M. Haughton and J.S. Hyde [1995], Functional Connectivity in the Motor Cortex of Resting Human Brain Using Echo-Planar Mri. *Magnet. Reson. Med.* **34**: 537-541.
- Buiatti, M., D. Papo, P.-M. Baudonnière and C. van Vreeswijk [2007], Feedback Modulates the Temporal Scale-free Dynamics of Brain Electrical Activity in a Hypothesis Testing Task. *Neuroscience* **146**: 1400-1412.
- Buiatti, M. and M. Buiatti [2008], Chance vs. Necessity in Living Systems: A False Antinomy. *Riv. Biol. / B. Forum* **101**: 29-65.
- Buzsaki, G. and A. Draguhn [2004], Neuronal Oscillations in Cortical Networks. *Science* **304**: 1926-1929.
- Damoiseaux, J.S., S.A.R.B. Rombouts, F. Barkhof, P. Scheltens, C.J. Stam, S.M. Smith and C.F. Beckmann [2006], Consistent Resting-state Networks across Healthy Subjects. *Proc. Natl. Acad. Sci. USA* **103**: 13848-13853.
- Debener, S., M. Ullsperger, M. Siegel and A.K. Engel [2006], Single-trial EEG-fMRI Reveals the Dynamics of Cognitive Function. *Trends Cogn. Sci.* **10**: 558-563.
- Doesburg, S.M., A.B. Roggeveen, K. Kitajo, L.M. Ward [2008], Large-Scale Gamma-band Phase Synchronization and Selective Attention. *Cereb. Cortex* **18**: 386-396.
- Fox, M.D., A.Z. Snyder, J.M. Zacks and M.E. Raichle [2006], Coherent Spontaneous Activity Accounts for Trial-to-trial Variability in Human Evoked Brain Responses. *Nat. Neurosci.* **9**: 23-25.
- Fox, M.D. and M.E. Raichle [2007], Spontaneous Fluctuations in Brain Activity Observed with Functional Magnetic Resonance Imaging. *Nat. Rev. Neurosci.* **8**: 700-711.
- Fox, M.D., A.Z. Snyder, J.L. Vincent and M.E. Raichle [2007], Intrinsic Fluctuations within Cortical Systems Account for Intertrial Variability in Human Behavior. *Neuron* **56**: 171-184.
- Gonzalez Andino, S.L., G. Thut, T. Landis and R. Grave de Peralta [2005], Prediction of Response Speed by Anticipatory High-frequency (Gamma Band) Oscillations in the Human Brain. *Human Brain Mapping* **24**: 50-58.
- Greicius, M.D., B. Krasnow, A.L. Reiss and V. Menon [2003], Functional Connectivity in the Resting Brain: A Network Analysis of the Default Mode Hypothesis. *Proc. Natl. Acad. Sci. USA* **100**: 253-258.
- Hausser, M., I.M. Raman, T. Otis, S.L. Smith, A. Nelson, S. du Lac, Y. Loewenstein, S. Mahon, C. Pennartz, I. Cohen, *et al.* [2004], The Beat Goes On: Spontaneous Firing in Mammalian Neuronal Microcircuits. *J. Neurosci.* **24**: 9215-9219.

- He, B.Y.J., A.Z. Snyder, J.M. Zempel, M.D. Smyth and M.E. Raichle [2008], Electrophysiological Correlates of the Brain's Intrinsic Large-scale Functional Architecture. *Proc. Natl. Acad. Sci. USA* **105**: 16039-16044.
- Hesselmann, G., C.A. Kell, E. Eger and A. Kleinschmidt [2008], Spontaneous Local Variations in Ongoing Neural Activity Bias Perceptual Decisions. *Proc. Natl. Acad. Sci. USA* **105**: 10984-10989.
- Jensen, O. and L.L. Colgin [2007], Cross-frequency Coupling between Neuronal Oscillations. *Trends Cogn. Sci.* **11**: 267-269.
- Kenet, T., D. Bibitchkov, M. Tsodyks, A. Grinvald and A. Arieli [2003], Spontaneously Emerging Cortical Representations of Visual Attributes. *Nature* **425**: 954-956.
- Laufs, H., K. Krakow, P. Sterzer, E. Eger, A. Beyerle, A. Salek-Haddadi and A. Kleinschmidt [2003], Electroencephalographic Signatures of Attentional and Cognitive Default Modes in Spontaneous Brain Activity Fluctuations at Rest. *Proc. Natl. Acad. Sci. USA* **100**: 11053-11058.
- Leopold, D.A., Y. Murayama and N.K. Logothetis [2003], Very Slow Activity Fluctuations in Monkey Visual Cortex: Implications for Functional Brain Imaging. *Cereb. Cortex.* **13**: 422-433.
- Linkenkaer-Hansen, K., V.V. Nikouline, J.M. Palva and R.J. Ilmoniemi [2001], Long-range Temporal Correlations and Scaling behavior in Human Brain Oscillations. *J. Neurosci.* **21**: 1370-1377.
- Linkenkaer-Hansen, K., V.V. Nikulin, S. Palva, R.J. Ilmoniemi and J.M. Palva [2004], Prestimulus Oscillations Enhance Psychophysical Performance in Humans. *J. Neurosci.* **24**: 10186-10190.
- Mantini, D., M.G. Perrucci, C. Del Gratta, G.L. Romani and M. Corbetta [2007], Electrophysiological Signatures of Resting State Networks in the Human Brain. *Proc. Natl. Acad. Sci. USA* **104**: 13170-13175.
- Melloni, L., C. Molina, M. Pena, D. Torres, W. Singer and E. Rodriguez [2007], Synchronization of Neural Activity across Cortical Areas Correlates with Conscious Perception. *J. Neurosci.* **27**: 2858-2865.
- Miltner, W.H.R., C. Braun, M. Arnold, H. Witte and E. Taub [1999], Coherence of Gamma-band EEG Activity as a Basis for Associative Learning. *Nature* **397**: 434-436.
- Monto, S., S. Palva, J. Voipio and J.M. Palva [2008], Very Slow EEG Fluctuations Predict the Dynamics of Stimulus Detection and Oscillation Amplitudes in Humans. *J. Neurosci.* **28**: 8268-8272.
- Nir, Y., R. Mukamel, I. Dinstein, E. Privman, M. Harel, L. Fisch, H. Gelbard-Sagiv, S. Kipervasser, F. Andelman, M.Y. Neufeld, *et al.* [2008], Interhemispheric Correlations of Slow Spontaneous Neuronal Fluctuations Revealed in Human Sensory Cortex. *Nat. Neurosci.* **11**: 1100-1108.
- Pfurtscheller, G., and F.H.L. da Silva [1999], Event-related EEG/MEG Synchronization and Desynchronization: Basic Principles. *Clin. Neurophysiol.* **110**: 1842-1857.
- Posner, M.I. and M.E. Raichle [1998], The Neuroimaging of Human Brain Function. *Proc. Natl. Acad. Sci. USA* **95**: 763-764.
- Raichle, M.E., A.M. MacLeod, A.Z. Snyder, W.J. Powers, D.A. Gusnard and G.L. Shulman [2001], A Default Mode of Brain Function. *Proc. Natl. Acad. Sci. USA* **98**: 676-682.

- Raichle, M.E. and M.A. Mintun [2006], Brain Work and Brain Imaging. *Annu. Rev. Neurosci.* **29**: 449-476.
- Raichle, M.E. and A.Z. Snyder [2007], A Default Mode of Brain Function: A Brief History of an Evolving Idea. *NeuroImage* **37**: 1083-1090.
- Rodriguez, E., N. George, J.P. Lachaux, J. Martinerie, B. Renault and F.J. Varela [1999], Perception's Shadow: Long-distance Synchronization of Human Brain Activity. *Nature* **397**: 430-433.
- Sehatpour, P., S. Molholm, T.H. Schwartz, J.R. Mahoney, A.D. Mehta, D.C. Javitt, P.K. Stanton and J.J. Foxe [2008], A Human Intracranial Study of Long-range Oscillatory Coherence across a Frontal-occipital-hippocampal Brain Network During Visual Object Processing. *Proc. Natl. Acad. Sci. USA* **105**: 4399-4404.
- Tallon-Baudry, C., O. Bertrand and C. Fischer [2001], Oscillatory Synchrony between Human Extrastriate Areas During Visual Short-term Memory Maintenance. *J. Neurosci.* **21**: art. no.-RC177.
- TallonBaudry, C., O. Bertrand, C. Delpuech and J. Pernier [1996], Stimulus Specificity of Phase-locked and Non-phase-locked 40 Hz Visual Responses in Human. *J. Neurosci.* **16**: 4240-4249.
- Tsodyks, M., T. Kenet, A. Grinvald and A. Arieli [1999], Linking Spontaneous Activity of Single Cortical Neurons and the Underlying Functional Architecture. *Science* **286**: 1943-1946.
- Varela, F., J.P. Lachaux, E. Rodriguez and J. Martinerie [2001], The Brainweb: Phase Synchronization and Large-scale Integration. *Nat. Rev. Neurosci.* **2**: 229-239.
- Vincent, J.L., G.H. Patel, M.D. Fox, A.Z. Snyder, J.T. Baker, D.C. Van Essen, J.M. Zempel, L.H. Snyder, M. Corbetta and M.E. Raichle [2007], Intrinsic Functional Architecture in the Anaesthetized Monkey Brain. *Nature* **447**: 83-U84.
- Womelsdorf, T. and P. Fries [2007], The Role of Neuronal Synchronization in Selective Attention. *Curr. Opin. Neurobiol.* **17**: 154-160.
- Womelsdorf, T., J.M. Schoffelen, R. Oostenveld, W. Singer, R. Desimone, A.K. Engel and P. Fries [2007], Modulation of Neuronal Interactions through Neuronal Synchronization. *Science* **316**: 1609-1612.
- Zarahn, E., G.K. Aguirre and M. D'Esposito [1997], Empirical Analyses of BOLD fMRI Statistics .1. Specially Unsmoothed Data Collected under Null-hypothesis Conditions (vol. 5, p. 179, 1997). *Neuroimage* **6**: 71-72.